crystallizations from methylene chloride–methanol to give a very small amount of colorless plates, mp 146–148°. A qualitative ultraviolet spectrum showed the following maxima in ethanol: 384.5, sh 374, 358.5, 342, 328, 314, 300, 287, 277, and 268 mμ.

Alkaline Permanganate Oxidation of Tetrangulol.—Tetrangulol (0.37 g) was suspended in 100 ml of 1 *N* potassium hydroxide solution and heated to dissolve as much as possible. Potassium permanganate solid (7.5 g) was added in small portions while heating on the steam bath, and after an hour of additional heating, the suspension was allowed to stand at room temperature overnight. The excess permanganate was destroyed with methanol and the suspension was filtered and washed with 1 *N* sodium hydroxide solution. The water-clear filtrate was strongly acidified with hydrochloric acid and concentrated to about 25 ml. After cooling, the precipitated salts were filtered, and the filtrate was extracted with four 25-ml portions of ethyl acetate. After drying over anhydrous sodium sulfate, filtration, and evaporation, 0.208 g of a white powder was obtained which was dissolved in 5 ml of concentrated nitric acid and heated for 45 min on a hot plate. When the nearly clear solution had concentrated to about 1 ml, the flask was cooled and 55 mg of a crystalline precipitate separated; after two recrystallizations from concentrated HNO_3, the benzene-1,2,3,4-tetracarboxylic acid melted constantly at 233–236° (lit.[12] mp 236–238°). A 20-mg sample of the acid was esterified in the usual fashion with ethereal diazomethane generated from 300 mg of N-methyl-N′-nitro-N-nitrosoguanidine. After 5 min, the excess reagent was destroyed with dilute, aqueous acetic acid, and the ethereal solution was washed with 1 *N* base, followed by water, dried over anhydrous sodium sulfate, and was evaporated. The residue was purified by partition chromatography on 5 g of acid-washed diatomaceous earth using a system composed of hexane–ethyl acetate–methanol–water (80:20:16:6). The sixth and seventh hold-back volumes contained virtually all of the solid and these gave, after several crystallizations from methanol, needles of methyl benzene-1,2,-3,4-tetracarboxylate melting constantly at 128–129° (lit.[13] mp 130–131°). The well-known[13] formation of a purple color upon exposure of the crystals to light was observed with our sample as well.

As anticipated, sublimation of the acid produced an anhydride (infrared bands at 1800–1860 cm^{-1}) whose melting point behavior was complex and nonreproducible.

Synthesis of 8,11-Dimethoxybenz[*a*]anthraquinone.—A mixture of 460 mg of 3,6-dimethoxyphthalic anhydride (prepared by hydroysis of 3,6-dimethoxyphthalimide by an unpublished procedure of Dr. H. S. Corey of these laboratories) and 256 mg of naphthalene in 50 ml of tetrachlorethane was chilled and 534 mg of anhydrous aluminum chloride was added in small increments. After stirring overnight at room temperature, the dark suspension was poured onto ice and acidified with sulfuric acid. The solution was extracted into chloroform and the dried chloroform layers were concentrated to produce 211 mg of a dark oil. This gradually crystallized in part to give 46 mg of an acid. The acid was not purified further but was dissolved in 10 ml of 90% sulfuric acid and warmed 5 min on a steam bath. The solution was poured onto ice, the product was obtained by chloroform extraction, and the chloroform layers were washed with 5% sodium hydroxide solution, dried, and evaporated to produce 31 mg of an orange-red residue. The amorphous residue was crystallized from methylene chloride–methanol to give 18 mg of the desired benz[*a*]anthraquinone which did not melt below 325°. The ultraviolet spectrum in methanol showed maxima at 236, 280, and 430 mμ (log ε 4.14, 4.04, and 3.71).

Anal. Calcd for $C_{20}H_{14}O_4 \cdot 0.333H_2O$: C, 74.11; H, 4.55. Found: C, 74.05; H, 4.32.

Acknowledgment.—The authors are indebted to their co-workers in the Biochemical Research Section for carrying out the fermentations and bioassays and in the Organic Chemical Research Section for microanalyses and some of the spectra.

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[12] L. I. Smith and E. J. Carlson, *J. Am. Chem. Soc.*, **61**, 288 (1939).

[13] D. E. Read and C. B. Purves, *ibid.*, **74**, 117 (1952).

Alkaloids of the *Papaveraceae*. IV. *Argemone hispida* Gray and *A. munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Ownb.[1]

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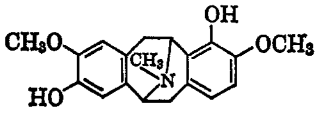
Received February 9, 1966

The alkaloid contents of *Argemone hispida* Gray and *A. munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Ownb. have been established and compared with other *Argemone* species in a search for biogenetic and chemotaxonomic relationships. A new alkaloid, munitagine, has been isolated from *A. munita* and its structure has been shown to be 2,7-dihydroxy-3,8-dimethoxy-5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene-N-methyl-6,12-imine. This represents the first alkaloid of the dibenzocyclooctene group to exhibit an altered substituent pattern.



The structures of all alkaloids of this group, including munitagine, can be correlated with that of reticuline, which was found to occur in both species.

The discovery and structure elucidation[1,4] of the interesting argemonine (5,6,11,12-tetrahydrodibenzo-[*a,e*]cyclooctene-N-methyl-6,12-imine) alkaloids (I) have provided new impetus for further investigations in some of the rarer genera of the poppy family. Since, with one exception,[4d] alkaloids of structure I have only been found in *Argemone* species, this genus seemed to provide the most fruitful place in which to search for new examples and to attempt to uncover biogenetic relationships. In addition, a recent excellent botanical monograph[5] critically reevaluates plant classifications and provides the comparison basis for chemotaxonomy

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[1] Part III: F. R. Stermitz and J. N. Seiber, *Tetrahedron Letters*, in press. The present study was presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

[2] Public Health Service Research Career Development Awardee (1-K3-GM-16, 698-01) of the National Institute of General Medical Sciences. This work was also supported by Grant GM-09300 from the NIGMS and Grant GB-1731 from the National Science Foundation.

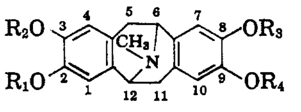
[3] National Institute of General Medical Sciences Public Health Service Predoctoral Fellow (5-F1-GM20, 217), 1963–1965.

[4] (a) M. J. Martell, Jr., T. O. Soine, and L. B. Kier, *J. Am. Chem. Soc.*, **85**, 1022 (1963); (b) F. R. Stermitz, S.-Y. Lwo, and G. Kallos, *ibid.*, **85**, 1551 (1963); (c) T. O. Soine and L. B. Kier, *J. Pharm. Sci.*, **52**, 1013 (1963); (d) R. H. F. Manske and K. H. Shin, *Can. J. Chem.*, **43**, 2180 (1965); (e) R. H. F. Manske, K. H. Shin, A. R. Battersby, and D. F. Shaw, *ibid.*, **43**, 2183 (1965).

[5] G. B. Ownbey, "Monograph of the Genus *Argemone* for North America and the West Indies," Memoirs of the Torrey Botanical Club, Vol. 21, The Seeman Printery, Durham, N. C., 1958.

studies. The suggestion was made by Slavik and Slavikova[6] that the species of *Argemone* can be divided into two groups depending upon the presence or absence of argemonine-type alkaloids. Interestingly, Ownbey[5] independently made tentative divisions of the genus based purely on plant morphology and these broadly follow the chemical characteristics.

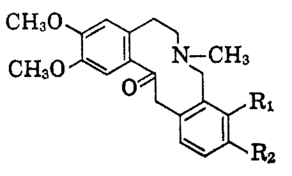
Four naturally occurring argemonine-type alkaloids have been previously characterized. Argemonine (Ia) was shown[4a,b] to be identical with the long-known synthetic compound N-methylpavine.[7] The structure of norargemonine (Ib) was proven[1] by synthesis, and that of bisnorargemonine (Id) as a result of its unique nmr spectrum.[4c] Eschscholtzine (Ie) was isolated[4d] from *Eschscholtzia californica* Cham. and its structure established.[4e] Eschscholtzine represents the only known occurrence of an argemonine-type alkaloid outside the genus *Argemone*. In the present study, the alkaloid contents of *A. hispida* Gray and *A. munita* Dur. & Hilg. subsp. *rotundata* (Rydb) G. B. Ownb. have been reexamined, and a new member of the group, munitagine, has been characterized.



Ia, R's = CH_3
b, $R_1 = H; R_2 = R_3 = R_4 = CH_3$
c, $R_2 = H; R_1 = R_3 = R_4 = CH_3$
d, $R_1 = R_4 = H; R_2 = R_3 = CH_3$
e, R_1 and $R_2 = CH_2$; R_3 and $R_4 = CH_2$

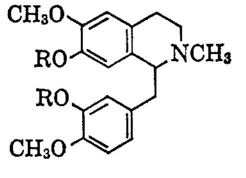
Results

Isolation of the Tertiary Alkaloids.—Extractions were carried out according to standard procedures using 1:1 butanol–benzene for the crude extraction and dilute, aqueous acid for the separation of the basic (tertiary alkaloid) components. *A. munita* subsp. *rotundata* gave a 0.44% yield of bases which was further divided by pH extraction into a nonphenolic (pH 12.5 extract) fraction and two phenolic fractions (pH 11.5 and 9.5 extracts). The two nonphenolic alkaloids, cryptopine (IIa) and muramine (IIb), were isolated from the pH 12.5 extract. Both are members of the protopine group of alkaloids and are widely distributed among the *Papaveraceae*.[8,9] The structure of muramine has been recently established as IIb from its nmr and mass spectra,[10a] and by synthesis.[10b]



IIa, $R_1 = R_2 = -OCH_2O-$
b, $R_1 = R_2 = OCH_3$

Further partitioning of the two phenolic extracts between pH 11.5 and 9.5 resulted in concentration of two bases in the pH 11.5 extract, the major component of which could be selectively precipitated as a solvent complex with carbon tetrachloride. Purification of this base proved difficult. The presence of a fraction having similar properties was noted in an early investigation of the species.[11] Eventually the base was crystallized from methanol–ether to yield the new compound (−)-munitagine ($C_{19}H_{21}NO_4$, mp 167–169°). Separation of the residual components in the carbon tetrachloride liquors by preparative tlc resulted in the isolation of a small amount of reticuline (IIIa), the first benzylisoquinoline alkaloid found among the *Argemone*. Reticuline was identified from its nmr spectrum, compared with that reported,[12] and by its conversion to laudanosine (IIIb) by methylation with diazomethane. The optical rotation ($[\alpha]^{27}D$ 33°, chloroform; +55°, ethanol) of the pure reticuline indicates that it is a mixture of (+)- and (±)-reticuline.[13] From the pH 9.5 extracts there were obtained relatively large quantities of the alkaloid (−)-bisnorargemonine (Id), the component previously isolated.[11] Contrary to a preliminary report,[4b] no argemonine was found in *A. munita*. An error was made in species correlation between our work[4b] and that of Soine.[4c]



IIIa, R = H
b, R = CH_3

Extraction of *A. hispida* Gray proceeded similarly, with the alkaloids fractionated by precipitation from aqueous ethanol and by pH extractions of the ethanol-soluble and -insoluble components. (−)-Argemonine (Ia) and (−)-norargemonine (Ib), the major components isolated previously,[14] were readily obtained and identified. In addition, small amounts of (−)-bisnorargemonine and reticuline (IIIa) were isolated from the pH 9.5 extract. The reticuline was identified in the same way as that obtained from *A. munita* and found to have the same optical rotation. A summary of the tertiary alkaloid components of *A. munita* subsp. *rotundata* and *A. hispida* is given in Table I. Traces of unidentified alkaloids were noted in the two species.

Determination of the Structure of Munitagine.—The nmr spectrum in deuteriochloroform (discussed later), together with the analyses of munitagine and its dibenzoate and O,O-dimethyl ether derivatives, established the empirical formula $C_{16}H_{10}(NCH_3)(OH)_2(OCH_3)_2$ for munitagine. The mass spectra (Table II) emphasized the close similarity of munitagine and

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[6] J. Slavik and L. Slavikova, *Collection Czech. Chem. Commun.*, **28**, 1728 (1963).

[7] A. R. Battersby and R. Binks, *J. Chem. Soc.*, 2888 (1955), and references contained therein.

[8] H.-G. Boit, "Ergebnisse der Alkaloid-Chemie Bis 1960," Akademie-Verlag, Berlin, 1961, p 347.

[9] H.-G. Boit and H. Flentje, *Naturwissenschaften*, **46**, 514 (1959); *ibid.*, **47**, 180 (1960; M. Maturova, B. K. Moya, J. Sitar, and F. Santavy, *Planta Med.*, **10**, 345 (1962); V. Preininger, P. Vacha, B. Sula, and F. Santavy, *ibid.*, **10**, 124 (1962).

[10] (a) A. D. Cross, L. Dolejs, V. Hanus, M. Maturova, and F. Santavy, *Collection Czech. Chem. Commun.*, **30**, 1335 (1965); (b) R. H. F. Manske, private communication.

[11] L. B. Kier and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 187 (1960).

[12] E. Brochmann-Hanssen and T. Furuya, *Planta Med.*, **12**, 328 (1964).

[13] E. Brochmann-Hanssen and B. Nielsen, *Tetrahedron Letters*, 1271 (1965).

[14] T. O. Soine and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **33**, 185 (1944).

TABLE I

THE ESTIMATED PERCENTAGE OF TOTAL OF THE TERTIARY ALKALOIDS OF *A. munita* SUBSP. *rotundata* AND *A. hispida*

Compd	Estimated per cent of total[a] *A. munita*	*A. hispida*
(−)-Argemonine (Ia)	...	45
(−)-Bisnorargemonine (Id)	65	5
Unidentified compounds, *Rf* 0.00, 0.55	<1	<1
Cryptopine (IIa)	2	...
(−)-Munitagine (VIII)	27	...
Muramine (IIb)	4	...
(−)-Norargemonine (Ib)	...	44
(+)-Reticuline (IIIa)	2	6

[a] Based on actual isolated amounts and estimated (by tlc analysis) composition of residue mixtures.

bisnorargemonine. The fragmentation of bisnorargemonine proceeds essentially by only one pathway, resulting in formation of the N-methylisoquinolinium ion (*m/e* 190). Loss of the N-methyl radical from this ion gives the isoquinolinium ion (*m/e* 175). The mass spectrum of munitagine was remarkably similar to that of bisnorargemonine, with the base peak at *m/e* 190 representing either the same or an isomeric N-methylisoquinolinium ion. Few other distinguishing characteristics were evident.

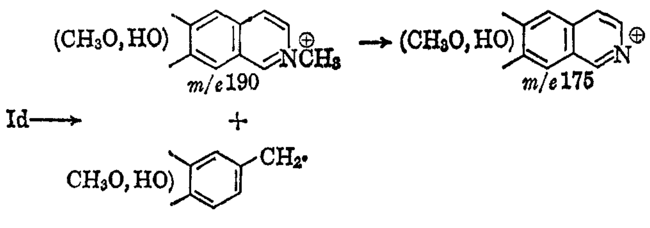


TABLE II

MAJOR PEAKS (WITH RELATIVE ABUNDANCES) IN THE MASS SPECTRA OF (−)-BISNORARGEMONINE AND (−)-MUNITAGINE

Compd	Parent	Base	Others[a]
Bisnorargemonine	327 (41)	190 (100)	328 (10), 326 (29), 312 (7), 192 (7), 191 (51), 177 (6), 175 (11), 147 (6), 118 (6), 115 (6)
Munitagine	327 (30)	190 (100)	328 (7), 326 (25), 312 (7), 192 (16), 191 (17), 177 (6), 175 (7), 156 (7), 147 (12), 145 (6)

[a] Those with *m/e* over 100 and having a relative abundance greater than 5.

Munitagine gave a positive color test with Gibb's reagent, indicating a phenol with a free *para* position. A negative test with alcoholic ferric chloride solution ruled out the possibility of a catechol function and a positive test with Millon's reagent indicated a phenol with a free *ortho* position. Since simple isomers of the known argemonine compounds would not be expected to give a positive Gibb's test, it appeared that a different oxygenation pattern was present on at least one ring. This was substantiated by the conversion of munitagine to an O,O-dimethyl ether which was different from argemonine (Ia), the ether expected if munitagine was a simple isomer of bisnorargemonine (Id), but having the same oxygenation pattern. O,O-Dimethylmunitagine was oxidized with potassium permanganate to a 1:1 mixture of hemipinic anhydride (IVa) and *m*-hemipinic anhydride (Va). The two anhydrides were separated and identified as their N-ethylimides (IVb and Vb) by the general procedure of Späth and Burger.[15] This established the structure of O,O-dimethylmunitagine as either VI or VII.

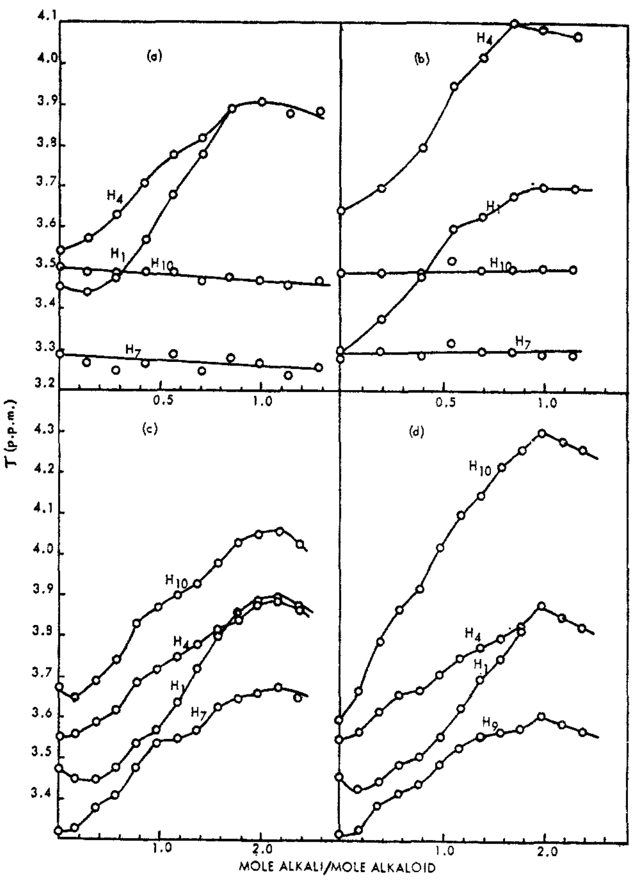
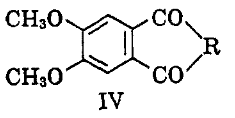
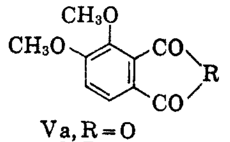


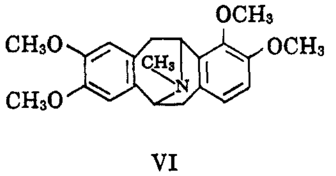
Figure 1.—Positional variation of the aromatic protons in the DMSO nmr spectra of (a) norargemonine (Ib), (b) isonorargemonine (Ic), (c) bisnorargemonine (Id), and (d) munitagine on conversion to their phenolic anion salts.



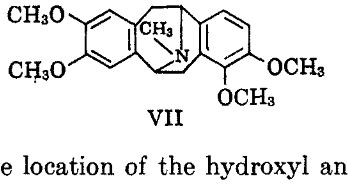
IV



Va, R = O
b, R = NC$_2$H$_5$



VI



VII

The relative location of the hydroxyl and methoxyl groups on munitagine was determined by using the nmr technique recently developed[16] and applied with some success to the same type of problem (*i.e.*, determi-

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[15] E. Späth and G. Burger, *Ber.*, **59**, 1486 (1926).

[16] (a) R. J. Highet and P. R. Highet, *J. Org. Chem.*, **30**, 902 (1965); (b) J. M. Brown, *Tetrahedron Letters*, 2215 (1964).

TABLE III

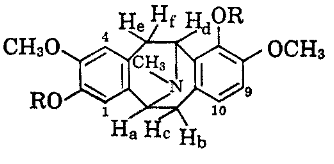
RANGES FOR THE ANION SHIFTS FOR THE AROMATIC PROTONS IN ALKALOID AND NONALKALOID PHENOLS (PPM)

Position	Nonalkaloid phenols[a]	Aporphines[b]	Argemonine alkaloids
ortho	0.42–0.59	0.47–0.54	0.41–0.48
meta	0.19–0.39	0.25–0.42	0.30–0.40
para	0.71–0.79	0.86	(0.70)[c]

[a] Reference 16a. [b] Reference 17a. [c] Only one example studied.

TABLE IV

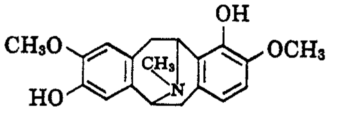
NMR SPECTRAL DATA FOR (–)-MUNITAGINE AND O,O-DIMETHYLMUNITAGINE IN DEUTERIOCHLOROFORM

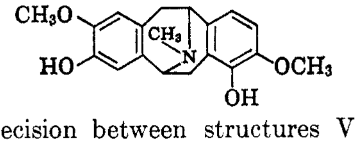


VIII, R = H
VI, R = CH3

	(–)-Munitagine (VIII)			O,O-Dimethylmunitagine (VI)		
Proton	τ	Coupling, cps	Splitting	τ	Coupling, cps	Splitting
H_a	6.07 (1)	$J_{ab} = 6$ $J_{ac} = 0$	Doublet	5.99 (1)	$J_{ab} = 6$ $J_{ac} = 0$	Doublet, part hidden
H_c	7.44 (1)	$J_{bc} = 17$	Doublet	7.37 (1)	$J_{bc} = 17$	Doublet
H_b, H_e	6.49 6.77 (2)	$J_{ab} = J_{de} = 6$ $J_{bc} = J_{ef} = 17$	Pair of doublets	6.45 6.73 (2)	$J_{ab} = J_{de} = 6$ $J_{bc} = J_{ef} = 17$	Pair of doublets
H_d	5.62 (1)	$J_{de} = 6$ $J_{df} = 0$	Doublet	5.66 (1)	$J_{de} = 6$ $J_{df} = 0$	Doublet
H_f	7.31 (1)	$J_{ef} = 17$	Doublet (part under NCH_3)	7.37 (1)	$J_{ef} = 17$	Doublet
OCH_3	6.18 (3) 6.24 (3)		Two singlets	6.06 (3) 6.20 (3) 6.15 (3) 6.23 (3)		Four singlets
NCH_3	7.47 (3)		Singlet	7.44 (3)		Singlet
H_1	3.40 (1)		Singlet	3.39 (1)		Singlet
H_4	3.59 (1)		Singlet	3.54 (1)		Singlet
H_9, H_{10}	3.38 (1) 3.52 (1)	$J = 8$	Pair of doublets	3.29 (2)	$J = 0$	Singlet
OH	*ca.* 4.0 (2)		Broad singlet	...		...

nation of the position of the phenolic OH) among the aporphines.[17] Proton chemical shifts in the aromatic regions of the nmr spectra of norargemonine (Ib), isonorargemonine (Ic), and bisnorargemonine (Id) were determined in dimethyl sulfoxide solution, then in solutions containing successive aliquots of base (sodium deuterioxide in deuterium oxide) until a slight excess of the amount of base needed for the conversion to the phenolate anion was present. The results are expressed in the curves shown in Figure 1. The curves for norargemonine (Ib) and isonorargemonine (Ic) were quite different, although the environments of H_1 and H_4 in these two molecules is altered only by the change of the relative positions of the hydroxyl and methoxyl groups in the same ring. H_1 in norargemonine and H_4 in isonorargemonine, the two protons *ortho* to the OH, undergo the greater upfield shift on conversion to the anion, as expected.[16,17] H_7 and H_{10}, the aromatic protons in the ring containing no OH, are little affected on conversion to the anion. The curve for bisnorargemonine (Id) is a composite of those for norargemonine (Ib) and isonorargemonine (Ic) as expected, since the environment about H_1 and H_4 for bisnorargemonine is the same as for the corresponding protons of norargemonine, while the environment about H_7 and H_{10} in bisnorargemonine is the same as for H_1 and H_4 in isonorargemonine. The curves for munitagine, determined in the same way, can be seen as partially comprised of those of norargemonine (Ib). Thus, the identity of the substitution patterns in one ring of norargemonine and in munitagine is established. The magnitude of the shift involved for one of the remaining aromatic protons (0.70 ppm) is characteristic for an aromatic proton *para* to a phenolic OH, while that for the other (0.30 ppm) is the same as that expected for a *meta* relationship. (See Table III.) These results allow the assignment of either structure VIII or IX to munitagine.





A final decision between structures VIII and IX for munitagine could be made in favor of VIII by analysis of the nmr spectrum. The spectra of munitagine (VIII) and its O,O-dimethyl derivative (VI), summarized in Table IV, are similar to those of argemonine (Ia)[4a] and eschscholtzine (Ie),[4e] but with some important differences. Being symmetrical, argemonine and eschscholtzine show two superimposable ABC systems for the protons corresponding to H_{a-c} and H_{d-f} (Table IV). The key to the structure of munitagine lies in a comparison of the bridgehead protons H_a and H_d. In the symmetrical alkaloids argemonine and eschscholtzine, these are represented by a doublet (two-proton integration) appearing at the lower field end (*ca.* τ 6.0) of the ABC system (H_d and H_a are each coupled to only one of the adjoining protons[4a]). Nor-

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[17] (a) K. G. R. Pachler, R. R. Arndt, and W. H. Baarschers, *Tetrahedron*, **21**, 2159 (1965); (b) W. H. Baarschers and K. G. R. Pachler, *Tetrahedron Letters*, 3451 (1965).

TABLE V

CHEMICAL SHIFT OF THE AROMATIC PROTONS OF ARGEMONINE AND MUNITAGINE AND THEIR DERIVATIVES

	τ values of protons at positions[a]			
Compd	1	4	7 or 9	10
(−)-Norargemonine (Ib)	3.38 (3.44)	3.58 (3.55)	3.38 (3.27)	3.58 (3.50)
(±)-Isonorargemonine (Ic)	3.41 (3.30)	3.53 (3.64)	3.41 (3.29)	3.53 (3.49)
(−)-Bisnorargemonine (Id)[b]	3.43 (3.47)	3.58 (3.55)	3.37 (3.32)	3.60 (3.67)
(−)-Munitagine (VIII)	3.40 (3.47)	3.59 (3.54)	3.38 (3.31)	3.52 (3.61)
(−)-Argemonine (Ia)	3.34 (3.30)	3.51 (3.52)	3.34 (3.30)	3.51 (3.52)
O,O-Dimethylmunitagine (VI)	3.39 (3.35)	3.54 (3.49)	3.29 (3.28)	3.29 (3.28)

[a] Values in deuteriochloroform are given first, followed by those in dimethyl sulfoxide in parentheses. [b] A few drops of dimethyl sulfoxide-d_6 was added to the deuteriochloroform solution to increase solubility.

argemonine (Ib) and bisnorargemonine (Id) are not completely symmetrical, but the asymmetry, caused by changes far removed from the bridgehead protons, is not sufficient to give these protons a different chemical shift, and a low-field doublet (*ca.* τ 6.0) integrating for two protons is again observed. However, the spectra of munitagine (VIII) and O,O-dimethylmunitagine (VI) show *two* low-field doublets, each integrating for one proton. One doublet appears at nearly the same chemical shift as in the other argemonine-type alkaloids (Ia–e) (*ca.* τ 6.0), while the second is shifted downfield considerably (*ca.* τ 5.6). These doublets are assigned to protons H_a and H_d, respectively, with H_a undergoing the greater downfield shift because of its proximity to the adjacent (on position 7) oxygen atom.[18] The alternate placement of substituents (IX) would result in little or no change in the chemical shift of the bridgehead proton. Structure VIII is thus established for munitagine. As will be dicussed below, this structure is easily correlated biogenetically with the other alkaloids of *A. munita*, while no reasonable metabolic pathway to IX seems to be available.

Analysis of the protons in the aromatic region is instructive and provides confirmatory evidence for the structure of munitagine. Aromatic protons H_9 and H_{10} exhibit an AB quartet in munitagine. This is difficult to see in deuteriochloroform solution, but is easily observed in dimethyl sulfoxide solution where some overlaying peaks are separated. In O,O-dimethylmunitagine, however, H_9 and H_{10} are not coupled and occur as a singlet. The chemical shifts for the aromatic protons of argemonine (Ia) and its O-demethyl derivatives (b–d) and for munitagine (VIII) and O,O-dimethylmunitagine (VI) are given in Table V for solutions in deuteriochloroform and dimethyl sulfoxide.

For the phenolic compounds (Ib–d and VIII) an upfield shift of 0.04–0.11 ppm is observed for the protons *ortho* and *para* to the OH on changing from deuterochloroform to dimethyl sulfoxide, while a downfield shift of 0.03–0.11 ppm is observed for the protons *meta* to the OH. The shifts for the nonphenolic compounds (Ia and VI) are less and occur in both directions.

The ultraviolet spectra of the argemonine-type alkaloids are not particularly useful for elucidation of structural details. However, the cyclohexane spectra (Figure 2) are distinctive and can serve, along with the characteristic nmr spectra, for rapid assignment of an unknown to this class. The maximum absorption for argemonine (Ia) and its O-demethyl derivatives (Ib–d), which appears as a broad peak at 280–290 mμ in ethanol and other polar solvents, is split into a well-defined multiplet in cyclohexane, with maxima at 294, 288, and 284 mμ. Except for slight deviations in the extinction coefficients, the curve in Figure 2a is applicable to all four compounds (Ia–d). The ultraviolet spectra of (−)-munitagine (VIII) and O,O-dimethylmunitagine (VI) (Figure 2b) are quite similar to those of argemonine and its O-demethyl derivatives (Figure 2a) except that, in the former, the splitting in the absorption maximum is not quite as pronounced and the extinction coefficients are lower.

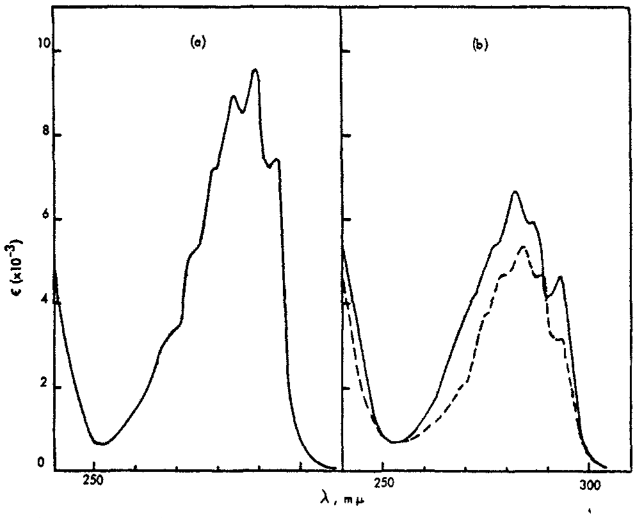

Figure 2.—The ultraviolet spectra in cyclohexane of (a) argemonine (Ia) and (b) munitagine VIII (———) and O,O-dimethylmunitagine VI (- - - -).

Discussion

Structural Relationships and Biogenesis.—Scheme I, shown below, presents the most likely biogenetic relationships among the alkaloids of *A. munita* and *A. hispida*. The structural relationships again point to a central role for reticuline (IIIa), as has been shown by numerous experiments by others in different genera of the poppy family. Particularly striking is the fact that the reticuline isolated from both *A. munita* and *A. hispida* contained, within experimental error, the same excess of (+)-reticuline over (±)-reticuline and that this excess is very close to that found in opium[13] and qualitatively similar to that in fresh *Papaver somniferum.*[19] Opium showed a 6:4 ratio of the optical isomers,[13] while we have found a ratio between 6:4 and 6:3. The values from *P. somniferum* plants directly were 6:1 for mature plants and 1:1 for seedlings.[19] Thus, it seems quite likely that the early precursor

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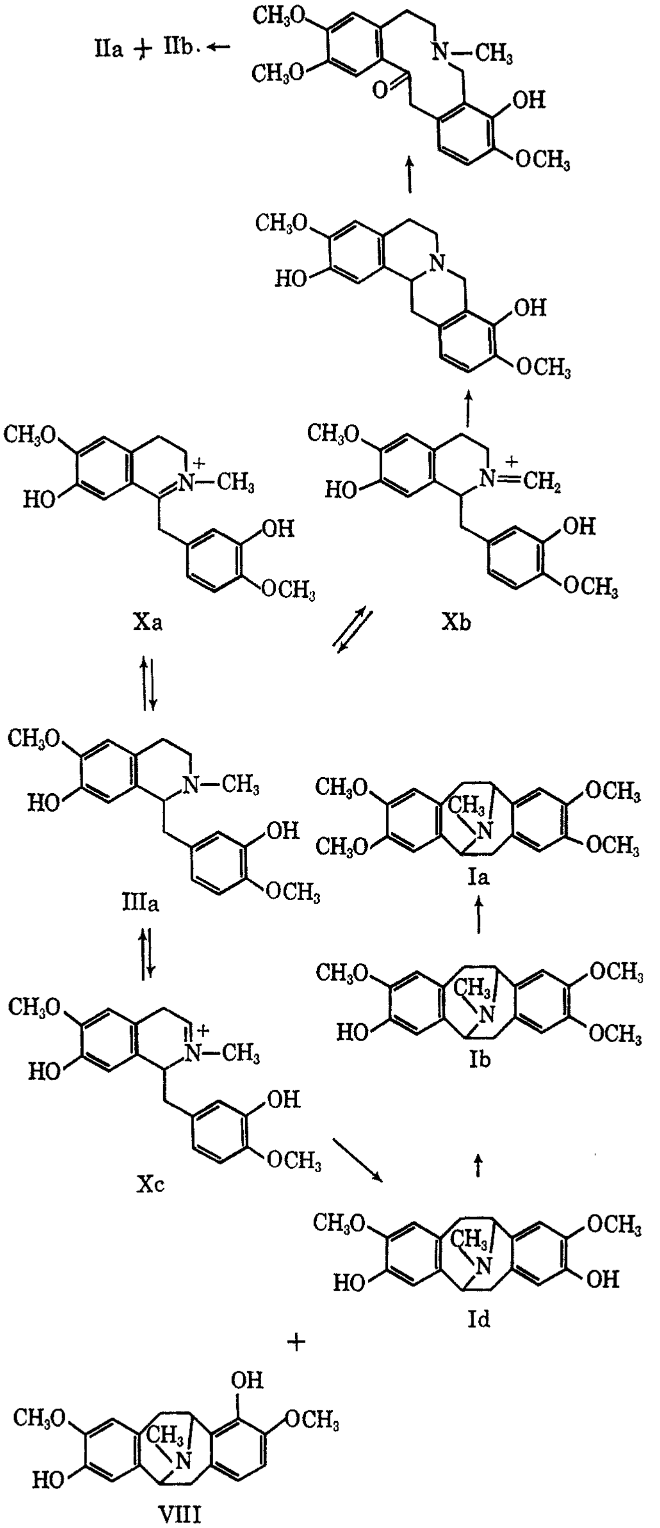
(18) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 102.

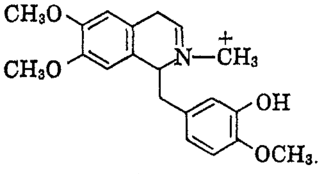
(19) A. R. Battersby, G. W. Evans, R. O. Martin, M. E. Warren, Jr., and H. Rapoport, *Tetrahedron Letters*, 1275 (1965).

SCHEME I



chemistry (to and including reticuline) in *P. somniferum, A. munita,* and *A. hispida* is very similar, if not identical.

The importance of reticuline appears to be further enhanced by a consideration of the structural relationships among the four argemonine-type alkaloids found in *A. munita* and *A. hispida*. Evidence has been presented[20] which points to an equilibrium between reticuline (IIIa) and iminium ion Xa in *P. somniferum*. Iminium ion Xb has been implicated[21,22] in the biosynthesis of protoberberine and protopine-type alkaloids. The suggested pathway to cryptopine (IIa) through Xb follows that already well substantiated by biosynthetic experiments.[21,22] If then, there is evidence pointing towards ions Xa and Xb, the intermediacy of Xc for further elaboration of the argemonine-type skeleton seems logical. This is the same type of intermediate suggested[7] to be involved in the synthesis of argemonine from N-methylpapaverinium salts. Although the relations between reticuline (IIIa) and ions Xb and Xc are here postulated as *equilibria*, there is no direct evidence for this other than analogy with the situation which apparently[20] exists between reticuline and Xa. It is also possible that ions X are interconvertible directly. The chief reason for suggesting that the argemonine-type alkaloids are formed directly from Xc is provided by our isolation of munitagine (VIII) along with bisnorargemonine (Id) in *A. munita*. Id and VIII represent, respectively, the products of *p*-phenol and *o*-phenol coupling reactions of Xc. This idea is strengthened by a consideration of the structure of norargemonine (Ib). If phenol coupling processes represent the driving force for formation of the argemonine-type alkaloids, then the phenolic group on the benzyl ring portion of Xc must be preserved. Hence, the only methylation process which could occur on Xc and still leave the possibility of phenol coupling would be the methylation of Xc to yield XI. Cyclization of XI, however, would yield isonorargemonine[1] (Ic) rather than norargemonine. Norargemonine is, therefore, most likely formed by methylation of bisnorargemonine and a second methylation would then yield argemonine (Ia).



XI

The only literature report of investigations in the biosynthesis of argemonine-type alkaloids is that of Barton and co-workers.[22] An insignificant incorporation of labeled (±)-reticuline into argemonine using mixed plants of *A. mexicana* and *A. hispida*[23] was reported. Radioactive analysis was done after dilution of the total basic fraction with inactive argemonine. A thorough study[24] of *A. mexicana* showed the presence of eight alkaloids, but no argemonine. A mixture of unknown amorphous nonphenolic basis was not iden-

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[20] A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 3323 (1965).

[21] A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, *Chem. Commun.*, 89 (1965).

[22] D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *J. Chem. Soc.*, 6379 (1965).

[23] This species, although "identified by Kew," was almost certainly not *A. hispida* Gray. Our analysis of true *A. hispida* Gray shows the presence of large amounts of both argemonine and norargemonine. In addition, we have not been able to germinate seeds of *A. hispida*. Ownbey has reported (private communication) that in his extensive study of hybridization in the *Argemone* genus he was able to germinate seeds of 20 out of 21 species, but was completely unsuccessful with the 21st: *A. hispida* Gray. In the early literature, *A. hispida* was often indiscriminately applied to various *Argemone* species. The Intermountain Herbarium at Utah State contains at least three different specimens labeled "*A. hispida*" which are obviously other species.

[24] L. Slavikova and J. Slavik, *Collection Czech. Chem. Commun.*, **21**, (1956).

tified, but this fraction represented only 7% of the total alkaloids present. It seems, therefore, that the insignificant incorporation[22] of reticuline into argemonine resulted because of an insignificant amount of argemonine in the plants investigated. True *A. hispida* Gray, as evidenced by our studies, represents an ideal plant in which to study argemonine-alkaloid biosynthesis because of the presence of reticuline, bisnorargemonine, norargemonine, and argemonine in the same plant. Since seed germination has been unsuccessful,[23] experiments with labeled precursors will be carried out in the field.

Experimental Section

All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Nashville, Tenn. Spectral instruments follow: infrared, Beckman Model IR-8; ultraviolet, Cary Model 15; nuclear magnetic resonance, Varian Model A-60. Mass spectral analyses were run by K. L. Rinehart of the University of Illinois and the Morgan Schaffer Corporation, Montreal. When organic solutions were dried, sodium sulfate was the drying agent. When organic solutions were evaporated to dryness, unless otherwise stated, a rotary evaporator was used with reduced pressure. Thin layer chromatography was conducted using silica gel G plates (250 μ) and a developing solvent of 3:2 benzene–methanol. Visualization was with iodoplatinic acid. Preparative plates (2000 μ) were used in the same way, except that only borders were visualized, and the desired bands were scraped off with a spatula. Optical rotations were obtained in chloroform, unless otherwise noted.

***Argemone munita* subsp. *rotundata*. Isolation of the Tertiary Alkaloids.**—Dried and powdered, largely overground plant parts from *A. munita*[25] (3.6 kg), harvested near Brigham City, Utah, in July 1965, were wetted with 7 l. of 10% sodium bicarbonate solution, then mixed with 15 l. of 1:1 butanol–benzene, in portions, in a Waring Blendor. After sitting several days, the mixture was filtered, the filter cake washed with additional 1:1 butanol–benzene, and the combined filtrate separated into an organic and aqueous layer. The organic layer was extracted with 10 l. of 2 *N* sulfuric acid, in portions, and the combined acid extracts made basic with excess aqueous ammonia and extracted with 8 l. of chloroform, in portions. Drying and evaporation of the combined chloroform extracts gave 16 g (0.44%) of the crude tertiary alkaloids[26] as a thick, brown syrupy solid. Analysis by tlc showed the presence of five bases, R_f 0.7, 0.55, 0.50, 0.40, and 0.20.

Preliminary Fractionation.—The total crude alkaloid extract was dissolved in 1200 ml of 2 *N* hydrochloric acid, the pH adjusted successively to 2.0, 12.5, 11.5, and 9.5 with aqueous potassium hydroxide solution and dilute hydrochloric acid, and extracted at each pH with chloroform (four 300-ml portions). Drying and evaporation of the chloroform extracts gave the results shown in Table VI.

TABLE VI

FRACTIONS FROM PRELIMINARY SEPARATION OF *A. munita* ALKALOIDS

pH fraction	Wt, g	R_f of tlc spots, with principal ones italicized				
2.0	0.45	*0.7*	0.55	*0.50*	0.40	
12.5	1.67	0.7	0.55	0.50	0.40	*0.20*
11.5	6.12	*0.7*	*0.50*	0.40		
9.5	5.81	0.7	*0.50*			

Treatment of the pH 12.5 Extract. Isolation of Cryptopine and Muramine.—The pH 12.5 extract was dissolved in 200 ml of 2 *N* hydrochloric acid, pH adjusted to 12.6 and 10.5 with aqueous potassium hydroxide solution and dilute hydrochloric acid, and extracted successively at each pH with chloroform (four 60-ml portions). Drying and evaporation of the chloroform gave 0.52 g of a dark residue from the pH 12.6 extract and 0.76 g from the pH 10.5 extract (the latter was combined with the pH 11.5 extract from above). The residue from this pH 12.6 extraction, after setting overnight in 15 ml of ethanol, deposited 0.25 g of crystalline material, containing mainly the bases, R_f 0.40 and 0.20. Separation of this solid on preparative tlc plates gave a fraction which yielded, after crystallization from methanol, 19.5 mg of crystalline cryptopine, mp 221–222° (lit.[8] mp 221°), R_f 0.40, identified by its spectral properties (nmr, infrared, ultraviolet). There was also obtained a fraction which yielded, after crystallization from ethanol, 48 mg of colorless muramine, mp 172–174° (lit.[9] mp 176–177°), identified by its spectral properties (mass, nmr, infrared, and ultraviolet).

Treatment of the pH 11.5 and 9.5 Extracts. Isolation of (−)-Bisnorargemonine.—The pH 11.5 and 9.5 extracts were partitioned between these two pH's by repeating the extractions with chloroform several times until the pH 11.5 extracts contained mainly the bases, R_f 0.70 and 0.40, and the pH 9.5 extracts contained mainly the bases, R_f 0.50 and 0.40. The residue from the pH 9.5 extracts then gave, after sitting several days in 90% aqueous ethanol, 5.22 g of colorless bisnorargemonine, mp 237–239°. A sample recrystallized from the same solvent had mp 243–246° (lit.[10] 245–245.5°), R_f 0.50, $[\alpha]^{27}\text{D}$ −222° (*c* 0.3) (lit.[10] $[\alpha]^{25}\text{D}$ −265.8°, methanol), with nmr infrared, and ultraviolet spectra in agreement with those reported.[4c,10]

Treatment of the pH 11.5 Extracts. Isolation of (−)-Munitagine.—The residue from the pH 11.5 extracts was triturated with 200 ml of warm carbon tetrachloride for several hours and filtered while warm. The residue removed by filtration was mainly bisnorargemonine, by tlc analysis. The liquor was concentrated to 100 ml and cooled (−15°) overnight. Filtration gave 2.32 g of amorphous powder containing mainly the base, R_f 0.70. The powder was heated with carbon tetrachloride, and the filtrate concentrated, cooled, and filtered to give 1.82 g of tan powder, mp 95–110°. Crystallization of this powder from 1:4 methanol–ether solution gave 1.30 g of crystalline solid, mp 128–140°. A sample recrystallized again from the same solvent gave munitagine as fine, colorless needles, mp 167–169°, R_f 0.70, $[\alpha]^{27}\text{D}$ −239° (*c* 0.5), $\nu_{\max}$ (KBr disk) 3580, 3470, 2950, 2870, 1620, 1500, 1455, 1370, 1335, 1285, 1250, 1123, 1080, 1135, 1020, 990, 960, 870, 828, 804, 783, 768, 730 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.50; H, 6.46; N, 4.36.

Reworking the mother liquors in the same way (extraction of residues with carbon tetrachloride, followed by crystallization of the resulting powders from methanol–ether) gave another 0.60 g of munitagine, mp 165–167°.

Isolation of (+)-Reticuline.—The carbon tetrachloride liquors from above were found to contain approximately a 3:1 mixture (by tlc analysis) of munitagine and the base, R_f 0.40. A 0.40-g portion of this mixture was separated on preparative tlc plates, yielding 44 mg of a fraction containing only the base, R_f 0.40. This material was dissolved in 100 ml of boiling *n*-heptane, and the solution filtered while hot, then cooled (−15°) for several hours. The resulting precipitate was collected and dried to give 19.6 mg of colorless amorphous powder, mp over a range to 90°, R_f 0.40, $[\alpha]^{27}\text{D}$ 33° (*c* 0.38), $[\alpha]^{27}\text{D}$ 55° (*c* 0.87, ethanol). It was identified as (+)-reticuline from its spectral properties (nmr and infrared) by comparison with those of an authentic sample of (±)-reticuline, prepared in the usual way[27] from its dibenzyl derivative,[28] and those reported in the literature.[12] A 15-mg sample of the (+)-reticuline was converted to (+)-laudanosine, $[\alpha]^{27}\text{D}$ 15° (*c* 0.84), identified by comparison with an authentic sample, by treatment with an ether solution of diazomethane. The (+)-laudanosine had $[\alpha]^{27}\text{D}$ 48° (*c* 0.48) after one recrystallization from Skellysolve A.

***Argemone hispida* Gray. Isolation of the Tertiary Alkaloids.**—The *A. hispida*[29] used in this study was harvested in eastern Wyoming in middle July, 1965. Crude extraction was carried out on 2575 g of largely overground plant parts with 1:1 butanol–benzene in the same way as for the *A. munita*. There resulted 15.6 g (0.61%) of crude tertiary alkaloids[22] as a nearly colorless

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[25] A voucher sample from this location is deposited at the Intermountain Herbarium, Utah State University, under No. 102032.

[26] The butanol–benzene and aqueous liquors were tested for completeness of extraction and the presence of quaternary alkaloids by evaporation of portions to dryness and examination of the residues. Only the aqueous extracts showed the presence of residual alkaloids, and these in insignificant quantities.

[27] M. K. Jain, *J. Chem. Soc.*, 2203 (1962).

[28] We wish to thank Professor H. Rapoport for a sample of dibenzylreticuline.

[29] Voucher samples are deposited in the Intermountain Herbarium, Utah State University under No. 107559 and 107560.

oily solid. Analysis by tlc showed the presence of five bases, R_f 0.75, 0.70, 0.50, 0.40, and 0.00.

Preliminary Fractionation.—The crude alkaloid extract was dissolved in 1200 ml of hot ethanol, 200 ml of water was added, and the solution cooled overnight to give 5.4 g of colorless solid, mp 220–238°. The liquor was evaporated to dryness, dissolved in 300 ml of 2 *N* sulfuric acid, the pH adjusted to 12.2 and 9.5 with aqueous potassium hydroxide solution and dilute sulfuric acid, and extracted at each pH with chloroform (four 100-ml portions). The results of these preliminary separations were as shown in Table VII.

TABLE VII

FRACTIONS FROM PRELIMINARY SEPARATION OF *A. hispida* ALKALOIDS

Fraction	Wt, g	R_f of tlc spots, with principal ones in italics			
(1) Solid, mp 220–238°	5.40	*0.75*	*0.70*		
(2) pH 12.2	8.13	*0.75*	*0.70*	0.40	0.00
(3) pH 9.5	1.55	0.70	*0.50*	*0.40*	0.00

Treatment of Fractions 1 and 2. Isolation of (−)-Norargemonine and (−)-Argemonine.—Fraction 2, the pH 12.2 extract, was dissolved in 75 ml of hot ethanol, cooled, and filtered to give 2.42 g of colorless solid, mp 200–220°. This was combined with fraction 1 (7.8 g total), the resulting mixture dissolved in 1 l. of 2 *N* sulfuric acid, and the pH adjusted first to 13.0 with aqueous potassium hydroxide solution, and extracted with ether (five 200-ml portions), and then to pH 9.5 with dilute sulfuric acid, and extracted with chloroform (five 200-ml portions). The chloroform extract was dried and evaporated to give 5.1 g of colorless solid which was recrystallized from 10:1 methanol–water to give 3.92 g of (−)-norargemonine as colorless cubes, mp 244–250° (lit.[14] 238°), R_f 0.70, $[\alpha]^{27}\mathrm{D}$ −151° (*c* 0.5) (lit.[30] $[\alpha]^{27}\mathrm{D}$ −154°), identified by comparison of its spectral properties (infrared and ultraviolet) with those reported.[30]

The ether extract of fraction 1 and the ethanol liquor from fraction 2 were combined, evaporated to dryness; the residue was dissolved in 900 ml of 2 *N* sulfuric acid. The acid solution was adjusted to pH 3.0, 12.6, and 9.5 with aqueous potassium hydroxide solution and dilute sulfuric acid, and extracted successively with chloroform (three 200-ml portions), ether (five 300-ml portions), and chloroform (five 200-ml portions), respectively. Drying and evaporation of the pH 12.6 ether extract gave 3.81 g of (−)-argemonine as its hydrate, mp 125–135° with effervescence (lit.[14] 130–140°), $[\alpha]^{27}\mathrm{D}$ −209° (*c* 0.5) (lit.[14] $[\alpha]^{24}\mathrm{D}$ − 214°, ethanol), identified by comparison of its spectral properties (nmr, infrared, and ultraviolet) with those reported.[4a,10]

Treatment of Fraction 3. Isolation of (−)-Bisnorargemonine and (+)-Reticuline. Fraction 3, the pH 9.5 extract, was dissolved in 25 ml of warm ethanol, the solution cooled (−20°) for 2 days, and filtered to give 0.15 g of (−)-bisnorargemonine as a crystalline solid, mp 244–246°, R_f 0.50, $[\alpha]^{27}\mathrm{D}$ −200° (*c* 0.378), identified by its spectral properties (nmr, infrared, and ultraviolet) and mixture melting point comparison with a sample of (−)-bisnorargemonine from *A. munita*.

The ethanol liquor was evaporated to dryness and the residue triturated with 50 ml of hot carbon tetrachloride several hours. The resulting mixture was filtered and the filtrate concentrated to 25 ml and cooled (−15°) overnight to give, after filtration, 0.65 g of a yellow powder, mp 65–80° (with effervescence) containing mainly the base, R_f 0.4, contaminated with small amounts of bisnorargemonine and norargemonine. A 0.15-g portion of this powder was separated by preparative tlc, and 53.1 mg of a fraction corresponding to pure base, R_f 0.4, was collected. This was dissolved in 50 ml of boiling *n*-heptane, filtered while hot, then cooled (−15°) overnight to give 42.6 mg of an oily solid precipitate. This material had $[\alpha]^{27}\mathrm{D}$ 33° (*c* 0.5), $[\alpha]^{27}\mathrm{D}$ 55° (*c* 0.8, ethanol), and was identified as (+)-reticuline from its spectral properties (nmr and infrared) as before. A 15-mg sample was converted into (+)-laudanosine, $[\alpha]^{27}\mathrm{D}$ 14° (*c*, 0.6), which had $[\alpha]^{27}\mathrm{D}$ 51° (*c* 0.5) after one recrystallization from Skellysolve A.

Chemical Examination of Munitagine.—Munitagine resisted efforts to prepare crystalline hydrochloride, hydrobromide, and methiodide salts in the usual ways. It formed a colorless dibenzoate derivative on treatment with benzoyl chloride in pyridine at 35° for 24 hr, mp 239–241°. The nmr spectrum (deuteriochloroform) had τ 1.6–3.0 (10 H, complex multiplet; 2 O-benzoyl groups), 3.10, 3.19, 3.42 (4 H, 3 singlets; 4 aromatics), 5.7–7.5 (6 H, complex multiplet partially hidden by OCH_3 and NCH_3; methylene–methine protons), 6.29, 6.33 (6 H, 2 singlets; 2 OCH_3), 7.5 (3 H, singlet; NCH_3). The infrared had ν_{max} (chloroform) 290, 1730, 1610, 1500 (doublet), 1440 (doublet), 1365, 1335, 1315, 1280, 1175, 1125, 1080, 1024, 905 cm^{-1}.

Anal. Calcd for $C_{33}H_{29}NO_6$: C, 74.00; H, 5.46; N, 2.62. Found: C, 73.34; H, 5.19; N, 2.72.

Munitagine gave a light green color with ethanolic ferric chloride solution (negative for catechol group), a deep blue color with Gibb's reagent, 2,6-dichloroquinone chloroimide (positive for a phenol with a free *para* position), and a red color with Millon's reagent (positive for a phenol with a free *ortho* position).

O,O-Dimethylmunitagine.—To a solution of 1.00 g of munitagine, mp 128–140°, in 90 ml of absolute methanol maintained at 0°, was added a solution of *ca* 2 g (eightfold molar excess) of diazomethane in 200 ml of dry ether. The resulting solution was allowed to warm slowly to room temperature over a period of 4 hr, then maintained at 30° for 15 hr. The solution was then evaporated to dryness and the residue dissolved in 25 ml of dilute hydrochloric acid. The acid solution was adjusted to pH 12.6 with aqueous potassium hydroxide and extracted with ether (four 20 ml portions). Drying and evaporation of the ether gave 0.97 g of a colorless glass, which crystallized from solution in 1:1 ether–Skellysolve A to give 0.59 g of product, mp 119–123°. A sample recrystallized from the same solvent had mp 124.0–125.5°, R_f 0.80, $[\alpha]^{27}\mathrm{D}$ −292° (*c*, 0.35), ν_{max} (KBr disk) 2950, 2860, 1610, 1510 (doublet), 1450, 1430, 1370, 1350, 1280, 1250 (doublet), 1220, 1135, 1110, 1080, 1040, 1015 (doublet), 990, 978, 873, 863, 847, 820, 785, 770, 732, cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.10; N, 3.94. Found: C, 70.82; H, 7.23; N, 4.07.

Oxidation of O,O-Dimethylmunitagine.—A solution of 0.400 g of O,O-dimethylmunitagine in 16 ml of 0.75 *N* hydrochloric acid solution was made basic by the addition of 2.9 g of potassium carbonate. The resulting mixture was heated to reflux and stirred as 3% potassium permanganate solution was added dropwise until the purple color of permanganate persisted (3 hr, *ca.* 2.25 g of potassium permanganate). The resulting mixture was cooled and sulfur dioxide passed through until a colorless solution was obtained. This solution was made definitely acidic with 1 ml of concentrated hydrochloric acid, evaporated to dryness on a rotary evaporator, and further dried in a desiccator over potassium hydroxide and phosphorous pentoxide. The resulting salt mixture was triturated with boiling acetone (three 100-ml portions), the acetone solution evaporated to dryness, and the residue sublimed (0.10 mm, 180°, 18 hr) to give 0.146 g of a mixture of oxidation product anhydrides as a yellow, oily sublimate. A portion of this sublimate (0.110 g) was evaporated to dryness on a steam bath with three 10-ml portions of a 33% solution of ethylamine in ethanol, and the residue sublimed (0.10 mm, 150°, 3 hr) to give 0.104 g of a mixture of oxidation product N-ethylimides as a yellow oily solid. The nmr spectrum (deuterochloroform) was virtually the same as that of a 1:1 mixture of authentic samples of N-ethyl-*m*-hemipinimde and N-ethylhemipinimide; 2.48, 2.90 (2 H, pair of doublets; *ortho* aromatics, J_{ab} = 7.5 cps), 2.71 (2 H, unsplit; *para* aromatics), 5.85, 6.05 (6 H, 2 sharp singlets; 2 O-methyl unsymmetrically substituted on benzene nucleus), 6.00 (6 H, unsplit; 2 O-methyl symmetriclly substituted on benzene nucleus), 6.30 (4 H, quartet; N–CH_2–CH_3), and τ 8.74 (6 H, triplet; N–CH_2–CH_3).

The mixture of oxidation product N-ethylimides was dissolved in 8 ml of boiling methanol, and the solution concentrated to 5 ml and cooled (0°) for several hours to give 23 mg of N-ethyl-*m*-hemipinimide as a yellow crystalline solid, mp 224–228°. A sample recrystallized from methanol had mp 228–233°, and gave no depression on admixture with an authentic sample, mp 233–235°, prepared by oxidation of (−)-argemonine.[30]

The residue, after evaporation of methanol, was evaporated to dryness on a steam bath with two 5-ml portions of a 33% solution of ethylamine in ethanol, and the residue sublimed (0.5 mm, 130°, 12 hr). The yellow sublimate was triturated with 4 ml of cold methanol and the solution was filtered to remove another 4 mg of

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(30) W. Schermerhorn and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 19 (1951).

impure N-ethyl-*m*-hemipinimide, and evaporated to dryness. The residue was dissolved in 5 ml of dry ether, 5 ml of Skellysolve A was added, and the solution was concentrated slowly to give a yellow liquor and oily precipitate. The liquor was further diluted with Skellysolve A and allowed to concentrate slowly during the course of several days to give 10 mg of a crystalline precipitate, mp 75–85°, which was proved identical with authentic N-ethylhemipinimide, mp 87–90°, prepared from the corresponding acid (K and K Laboratories, Inc.), by comparison of their infrared spectra in potassium bromide.

Studies Leading to the Stereoselective Total Synthesis of *dl*-β-Eudesmol, *dl*-β-Selinene, *dl*-Costol, and Related Naturally Occurring Sesquiterpenes

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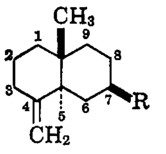
The key intermediate in these synthetic studies, *trans*-8-methylene-10-methyl-2-decalone (**7**), was prepared from 10-methyl-1(9)-octal-2-one (**1**) by a six-step sequence. The ketal derivative **2** of octalone **1** afforded the *cis*-fused hydroxy ketal **3** upon hydroboration and oxidation. The corresponding *cis*-decalone **4** was converted to the *trans* isomer **5** *via* acid- or base-catalyzed equilibration and the methylene derivative **6** was prepared from this ketone using methylenetriphenylphosphorane in dimethyl sulfoxide. This same methylene decalin (**6**) resulted when the *cis*-decalone **4** was similarly treated. Hydrolysis afforded the corresponding decalone **7**. The *trans* ring fusion of decalone **7** was confirmed through independent synthesis of its dihydro derivative **12** from *trans*-8,10-dimethyl-1(9)-octal-2-one (**8**) *via* hydrogenation of the related octalol **10** and oxidation of the resulting decalol **11**. Decalol **18**, prepared from decalone **7** using lithium aluminum hydride, was converted to the nitrile **20** through its *p*-toluenesulfonate derivative **19**. The related acid **21** was obtained through saponification of nitrile **20**. Addition of methyllithium to the methyl ester **22** of acid **21** afforded racemic β-eudesmol (**23**). Additional evidence for the stereochemical assignments of nitrile **20** and acid **21** was secured through a study of the synthesis and saponification of the isomers of *trans*-10-methyldecalin-2-nitrile, **26** and **30**, prepared from appropriate sulfonates of alcohols **24** and **28**. The synthesis of β-selinene was effected by the condensation of *trans*-2β-acetyl-8-methylene-10β-methyldecalin (**31**) with methylenetriphenylphosporane in dimethyl sulfoxide. Ketone **31**, which was obtained through addition of methyllithium to nitrile **20** and hydrolysis of the intermediate imine, also yielded β-eudesmol (**23**) upon treatment with methyllithium. Costol (**37**) was synthesized *via* reduction–elimination of the enolate of malonic ester **36** with lithium aluminum hydride. Ester **36** was stereoselectively prepared from the methanesulfonate derivative **35** of decalol **34** which was secured by formolysis of the *p*-toluenesulfonate **19** in moist N,N-dimethylformamide and saponification of the formate **33** thereby obtained. Costal (**39**) and costic acid (**40**), two naturally occurring relatives of costol, were prepared by successive oxidation of costol with manganese dioxide and silver oxide.

The eudesmane group of sesquiterpenes[2] confronts the student of organic synthesis with a variety of interesting problems. β-Eudesmol, an example of the simpler structural types to be found in this group, is noteworthy for its role in the stereochemical correlation of terpenes and steroids.[3] The carbon framework of β-eudesmol, including the C-4 exocyclic methylene grouping, reappears in a number of its close relatives such as β-selinene,[4] costol,[5] costal,[6] and costic acid.[7] Since these compounds differ only in the substitution pattern of their C-7 isopropyl side chains, we felt that all might conceivably be amenable to synthesis from the same intermediate. In this report we describe one such intermediate, *trans*-10-methyl-8-methylene-2-decalone (**7**), and illustrate its utility in the synthesis of racemic counterparts of the aforementioned sesquiterpenes.[8]



β-eudesmol, $R = (CH_3)_2COH$
β-selinene, $R = CH_2{=}CCH_3$
costol, $R = CH_2{=}CCH_2OH$
costal, $R = CH_2{=}CCHO$
costic acid, $R = CH_2{=}CCO_2H$

Chart I outlines the sequence employed for the synthesis of decalone **7**. The readily available bicyclic ketone, 10-methyl-1(9)-octal-2-one (**1**)[9] afforded the ethylene ketal derivative **2** upon treatment with ethylene glycol in either refluxing benzene or toluene containing *p*-toluenesulfonic acid. Although we were unable to force this reaction to completion, relatively pure ketal **2** could be secured by crystallization of the crude product at low temperature. The material thus obtained gave rise to an unresolved triplet at 5.23 ppm (vinyl hydrogen) in its nmr spectrum in accordance with the expected double bond migration from the $\Delta^{1(9)}$ to the Δ^{8} position during ketalization.[10] Hydroboration, followed by oxidation of the resulting organoborane with alkaline hydrogen peroxide,[11] provided the means for converting unsaturated ketal **2** to hydroxyl ketal **3**. We expected the *cis*-fused hydroxy ketal **3** to predominate on steric grounds since the axial oxygen of the ketal grouping in **2** appears to effectively block the

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